(c) a C_{max}, dose value (in (nmol/L)/(mg/kg)) of from 60 to 310, upon administration of a dose (in mg/kg) of N-benzoylstaurosporine.

REMARKS

Claim 11 has been amended to clarify and more completely claim the subject mater which the Applicants have disclosed. Support for the amendment to claim 11 may be found in the Specification on page 13 lines 17–25).

The Examiner has stated that the Applicant's have not filed a certified copy of the United Kingdom application 9903547.9 under which they claim priority under 35 U.S.C. § 119 (a)-(d). The Applicants respectfully assert that the present application filing on August 15, 2001, contains both a submission stating a claim for priority under 35 U.S.C. §119 and also a certified copy of the application UK 9903547.9. The submission and certified copy were received in the USPTO on August 15, 2001. A copy of the stamped postcard from the USPTO and the cover sheets of UK 9903547.9 are enclosed for verification of the previous filing. The Applicants respectfully request that the Examiner verify that the submission and certified copy were received in the present application.

The Examiner has stated that the reference WO 94/09211, which is incorporated by reference in the present application in order to describe how to obtain claimed lipophilic components, is incorrect noted in the Specification. The application WO 94/09211 is drawn to a "Soundproofing Member and Use Thereof". Since the method of obtaining the claimed lipophilic components is described in GB 2257359, which is also incorporated by reference, the Applicants respectfully request that the words "or WO 94/09211" be deleted from page 11 lines 25 and 28 of the Specification.

The Examiner has rejected claims 1-2, 4-6, and 8 under 35 USC § 102(b) as being anticipated by Weder, et al. (US 5658898). The Examiner claims that N-benzoyl staurosporine, a hydrophilic component (e.g. sorbitan, mannitol, glucose, etc.), purified lecithin (e.g. LIPOID S 100), a fatty acid triglyceride (e.g. Miglyol 812) and polyoxyethylene sorbitan (e.g. TWEEN) are taught or suggested by Weder '898. The Examiner also believes that the HLB values claimed in the present application are anticipated by Weder's disclosure of TWEEN and Milgyol 812.

The Applicants respectfully disagree with the Examiner and request that the rejection of claims 1-2, 4-6, and 8 be withdrawn. The Applicants' invention is drawn to compositions of different elements than Weder '898.

In Weder '989, the compositions claimed therein are formulated as dispersions in water for injection contrary to the compositions claimed in the present invention. The present invention claims a composition comprised of an N-benzoyl staurosporine, a hydrophilic component and a surfactant. In claim 1 of Weder '898, the compositions claimed therein require liquid water as a carrier in addition to the active ingredient and other excipients (see US 5,658,898 claim 1 element e)). The Applicants' present invention omits water from the composition and yet, surprisingly, is able to be spontaneously dispersed in the gastric environment.

The novelty of the Applicants' invention is further exemplified by the absence of a complex process for preparation of the dispersion as described in Weder '898 (see column 9 lines 15 - 47). The Applicants compositions are formulated in a conventional manner, such as simple mixing, which would be readily apparent to one skilled in the art, or as a micellar precursor such as simple colloids (see Specification page 10 lines 21 – 24 and page 4 line 10). Weder '898 describes a complicated process for preparation of an oily suspension, an aqueous liposome dispersion, and the use of high pressure homogenisation to create a nanoemulsion in order to prepare the composition claimed therein so that it is aqueously pre-dispersed prior to administration.

The Applicants assert that Weder '898 does not anticipate the Applicants' present invention. The Applicants' present composition does not claim water as a required element and formulation requirement. The Applicants have surprisingly determined a mixture of agents which solubilize N-benzoylstauropsorine and create a formulation which spontaneously disperses in the gastric environment. Thus, the Applicants respectfully request that the Examiner withdraw the rejection of claims 1-2, 4-6, and 8 under 35 USC § 102(b) as being anticipated by Weder, et al. (US 5658898).

The Examiner has rejected claims 1-4 and 6 under 35 USC § 102(e) as being anticipated by Weder, et al. (US 5726164). The Examiner believes that Weder '164 teaches or suggests an N-benzoyl staurosporine, a hydrophilic component (e.g. ethanol and water), polyoxyethylene/polyoxypropylene block copolymer (e.g. Pluronic F68 and Lutrol F68) and phospholipids, in lecithin (LIPOID S 100) and anticipates these claims. The Applicants respectfully disagree with the Examiner and request that the rejection be withdrawn. In contrast to the Applicants' present invention Weder '164 requires water for the composition claimed therein (see US 5726164 claim 1 element c)). The compositions of Weder '164 are sterile aqueous infusions for intravenous use or dry preparations which must be re-constituted for aqueous infusion (see claims 1 and 10). As discussed above for Weder '898, the invention of Weder '164 claims and discloses an oral formulation which requires water for formulation. The Applicants have invented an oral formulation of N-benzoylstaurosporine that does

not require water for formulation and is surprisingly stable and spontaneously dispersible in the gastric environment. Thus, the Applicants respectfully request that the rejection be withdrawn.

The Examiner has rejected claim 7 under 35 USC § 103(a) as being obvious over Weder (US 5726164) in view of Henry, et al. (US 5736542). The Applicants respectfully disagree with the Examiner and request that the rejection be withdrawn. The Applicants have discussed above that Weder '164 is not anticipatory of the present invention because of differing elements and formulation required for the respective inventions. Thus, Weder '164 differs in more respects from the Applicants' invention than the omission of transesterified ethoxylated vegetable oil. The present invention also does not require the element of water, as does Weder '164. In addition, the present invention also claims and discloses an oral formulation which is in liquid phase so as to be spontaneously dispersible in the gastric environment. Weder '164 discloses an aqueous dispersion for intravenous administration. For oral delivery, Henry '542 discloses and claims a composition of a solution or dispersion that is either in a solid dispersion (see column 2 lines 28-47 and claim 1) or may be in an aqueous dispersion that is formed by dissolving the solid dispersion in an aqueous medium (see column 2 lines 48-54). Henry '542 have not disclosed or claimed an invention which teaches or suggests the Applicants invention. The Applicants have disclosed and claimed a spontaneously dispersible oral non-solid composition for N-benzoylstaurosporine. Thus, it would not be obvious to one skilled in the art to combine the teachings of Weder '164 with Henry '542 since they are drawn to compositions with different physical states, different routes of administration and different required elements than the Applicants' invention. There is no motivation in Weder '164 or Henry '542 that the teachings therein may be combined to make oral, non-solid, compositions which do not contain water (Weder) and which are spontaneously dispersible in the gastric environment. The Applicants therefore request that the Examiner withdraw his rejection on these grounds.

The Examiner has rejected claims 9 and 11 under 35 USC § 103(a) as obvious over Weder (US 5726164). The Examiner states that the optimization of known active and inactive ingredients in a composition is well considered within the skill of the artisan thus rendering the present invention obvious. The Applicants respectfully disagree with the the Examiner and respectfully request that the rejection of claims 9 and 11 be withdrawn.

The Examiner appears to be stating that it would be obvious to try the present combination of elements. The Applicants have herein above discussed that the present invention is drawn to orally administered compositions of N-benzoylstaurosporine which do not require the element of water for formulation and which are spontaneously dispersible in the gastric environment. The invention of

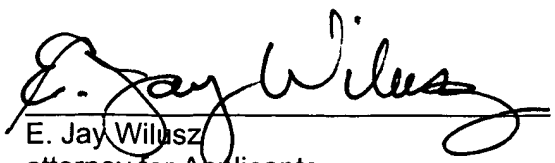
Weder '164 discloses and claims an aqueous dispersion for intravenous administration. The Applicants' surprising results of enhanced gastric dispersion with the ratios of excipients of claim 9 can not be derived from or attributed to the pre-dispersed injectable formulation of Weder '164. Weder '164 in fact state that oral forms for staurosporine derivatives cause disadvantages, such as gastro-intestinal (so-called "first-pass") metabolism and absorption, that may be overcome with injectable forms such as those claimed in Weder '164 (see column 1 lines 44-61). Weder '164 teach away from the present invention and do not render obvious the Applicants optimized composition in claim 9. Similarly, the orally bioavailable nature of the Applicants present invention as claimed in claim 11 would not be obvious to one skilled in the art from the contrary teachings of Weder '164. The Applicants have determined content and ratios of excipients in order to provide an enhanced and bioavailable spontaneously dispersable composition for oral delivery of N-benzoylstaurosporine which is not taught or suggested by Weder '164. The Applicants therefore, respectfully request that the Examiner withdraw the rejection of claims 9 and 11.

Attached hereto is a marked-up version of the changes made to the specification and claim 11 by the current amendment. The attached page is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

Entry of this amendment is respectfully requested. In light of the foregoing, the Applicants assert that they believe the Application is in condition for allowance and request early notice to that effect. If it will advance prosecution of this application the Examiner may phone the Applicants' undersigned counsel at the phone number listed below.

It is not believed that any fees are due in this case however, the USPTO is authorized to charge any further fees that are properly assessable in this case or credit any overpayment to Deposit Account No. 19-0134.

Respectfully submitted,



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Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6742

Date: Oct. 23, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Deleted: - - or WO 94/09211 - - from page 11 lines 25 and 28.

IN THE CLAIMS:

11. (Amended) A pharmaceutical composition for oral administration comprising N-benzoylstaurosporine and having
(a) a variability of bioavailability levels of N-benzoylstaurosporine of from 5 to 17%;
(b) an AUC (0-48h)/dose value (in (h·nmol/L)/(mg/kg)) of from 380 to 2000, or
(c) a C_{max}, dose value (in (nmoJ/L)/(mg/kg)) of from 60 to 310, upon administration of a dose (in mg/kg) of N-benzoylstaurosporine ~~in fasted beagle dogs~~.

CASE 4-30811A/C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

OIPE JC182 OCT 23 2002 PATENT & TRADEMARK OFFICE

RECEIVED OCT 28 2002 TECH CENTER 1600/2900

IN RE APPLICATION OF
MATTHEWS ET AL.
APPLICATION NO: N/A
FILED: Herewith
FOR: SPONTANEOUSLY DISPERSIBLE N-BENZOYL STAUROSPORINE COMPOSITIONS

Assistant Commissioner for Patents
Washington, DC 20231

CLAIM OF PRIORITY UNDER 35 USC §119

Sir:

Applicants in the above-identified application hereby claim priority under the International Convention of British Application No. 9903547.9, filed on February 16, 1999. This application is acknowledged in the Declaration of the instant case.

The certified copy of said British application is submitted herewith.

Respectfully submitted,

Norbert Gruenfeld
Agent for Applicants
Reg. No. 30,061

Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6921
Date: August 14, 2001

The Patent Office

11-30811 P1

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Andrew Gerry

Dated 8 December 1999

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Patents Act 1977
(Rule 16)

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference: 4-30811/P1

9903547.9

16 FEB 1999

1FEB99 E425996-4 000524 P01/7700 0.00 - 9903547.9

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*:
NOVARTIS AG
SCHWARZWALDALLEE 215
4058 BASEL
SWITZERLAND

Patent ADP number *(if you know it)*: 7125487002

If the applicant is a corporate body, give the country/state of its incorporation: SWITZERLAND

4. Title of invention: Organic compounds

5. Name of your agent *(If you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*:
B.A. YORKE & CO.
CHARTERED PATENT AGENTS
COOMB HOUSE, 7 ST. JOHN'S ROAD
ISLEWORTH
MIDDLESEX TW7 6NH

Patents ADP number *(if you know it)*: 1800001

6. If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

(see note (d))

Yes

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Case No 4-30811 A/C1

Application No.

Mailing Date: Aug 15, 2001

Due Date: Aug. 16, 2001

Express Mail No.: EL 751039764 US

The Patent & Trademark Office acknowledges, and has stamped hereon the date of receipt of the items checked below:

- ☐ Amendment/Response/Letter - Fee $_____
- ☑ Appln. Filing Papers - Fee $790.-
  - ☐ PCT National Stage
  - ☐ Provisional Application
  - ☐ CPA ☐ DIV ☑ CONT ☐ CIP
  - ☑ Specification 23 Pg's
- ☑ Executed Unexecuted Decl. - Fee $_____
  - ☐ Missing Parts/Missing Req.:
- ☑ Preliminary Amendment 3 Pg's
- ☑ Claim of Priority ☑ Certified Copy(s) (1)
- ☐ Amendment After Final
- ☐ Notice of Appeal - Fee $_____
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